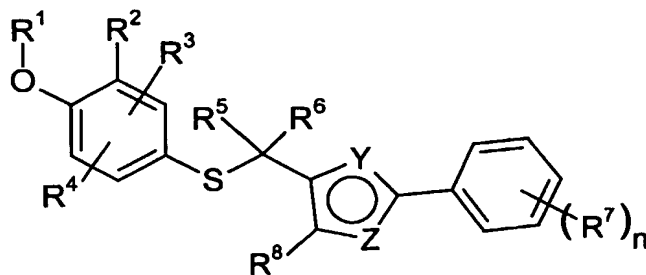


Claims

We claim:

1. A process for the preparation of a compound of formula (IV),

5



(IV)

wherein,

10 R¹ is selected from the group consisting of H, -Si(R⁹)₃, -C(R¹⁰F¹⁰)C(O)₂H, benzyl, allyl, and C₁₋₆alkyl;

R², R³, and R⁴ are independently selected from the group consisting of H, C₁₋₃alkyl, -OCH₃, -CF₃, allyl, and halogen;

15 R⁵ and R⁶ are independently selected from the group consisting of H, phenyl, benzyl, C₁₋₆alkyl, and allyl;

each R⁷ is independently -CF₃, C₁₋₃alkyl, -OCH₃, or halogen;

20 R⁸ is selected from the group consisting of H, -CF₃, and C₁₋₆alkyl;

one of Y and Z is N and the other is S or O;

25 each R⁹ is independently C₁₋₆alkyl, or arylC₁₋₆alkyl, or two R⁹ groups together with the silicon atom to which they are attached form a 5-7 membered ring;

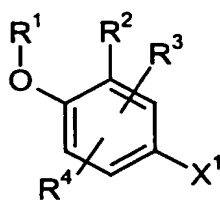
each R^{10} is independently H or C_{1-3} alkyl, or both R^{10} groups together with the carbon atom to which they are attached form a 3-6 membered ring; and

5 $n = 0, 1, 2, 3, 4, \text{ or } 5$;

said method comprising the steps of:

a) treating of a compound of formula (I) with an alkyl lithium reagent,

10 magnesium (0), or magnesium (0) followed by treating with a dihalo zinc (II) reagent,



(I)

15 wherein,

R^1 , R^2 , R^3 , and R^4 are as defined above; and

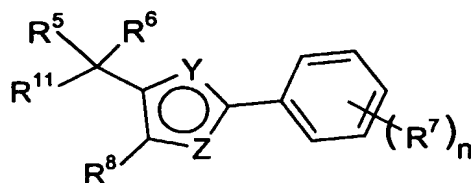
X^1 is selected from the group consisting of Cl, Br, and I;

20

b) followed by treating with sulfur; and

c) followed by treating with a compound of formula (III),

46



(III)

wherein,

R⁵, R⁶, R⁷, R⁸, Y, Z, and n are as defined above;

5

R¹¹ is Cl, Br, I, or $-\text{OS}(\text{O})_2\text{R}^{12}$; and

R¹² is selected from the group consisting of C₁₋₆alkyl, C₆₋₁₀aryl, C₆₋₁₀arylC₁₋₆alkyl, and $-\text{CF}_3$.

10

2. A process according to Claim 1, wherein said process is performed without isolation of intermediate compounds between steps (a) and (b) or (b) and (c).

3. A process according to either one of Claims 1 or 2, wherein R¹ is $-\text{Si}(\text{R}^9)_3$.

15

4. A process according to either one of Claims 1 or 2, wherein R¹ is $-\text{Si}(\text{CH}_3)_2t\text{-Bu}$.

5. A process according to either one of Claims 1 or 2, wherein R¹ is

20 $-\text{C}(\text{R}^{10}\text{R}^{10})\text{C}(\text{O})_2\text{H}$.

6. A process according to Claim 5, wherein R¹⁰ is $-\text{CH}_3$.

7. A process according to either one of Claims 1 or 2, wherein R¹¹ is Cl or $-\text{OS}(\text{O})_2\text{R}^{12}$, and R¹² is C₁₋₆alkyl.

25

8. A process according to either one of Claims 1 or 2, wherein:

R¹ is -Si(CH₃)₂*t*-Bu;

R² is -CH₃;

5 R³ and R⁴ are H;

R⁵ and R⁶ are H;

n is 2;

10

one R⁷ is fluorine in the *ortho* position and the other is -CF₃ is the *para* position;

R⁸ is -CH₃;

15

Y is S; and

Z is N.

20 9. A process according to either one of Claims 1 or 2, wherein:

R¹ is -C(R¹⁰R¹⁰)C(O)₂H;

R² is -CH₃;

25

R³ and R⁴ are H;

R⁵ and R⁶ are H;

30

n is 2;

one R⁷ is fluorine in the *ortho* position and the other is -CF₃ is the *para* position;

R^8 is $-\text{CH}_3$;

Y is S;

5

Z is N; and

each R^{10} is $-\text{CH}_3$.

10 10. A process according to Claim 8, said process further comprising the step cleaving the R^1 silyl group, to afford a compound of formula (IV), wherein R^1 is $-\text{H}$.

15 11. A process according to Claim 8, said process further comprising the steps of:

d) cleaving the R^1 silyl group to afford a compound of formula (IV), wherein R^1 is $-\text{H}$; and

20

e) treating with an alkylating agent to afford a compound of formula (IV), wherein R^1 is $-\text{C}(\text{R}^{10}\text{R}^{10})\text{C}(\text{O})_2\text{H}$, and R^{10} is $-\text{CH}_3$.

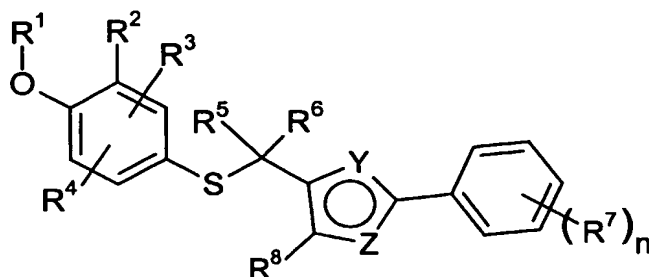
25 12. A process according to Claim 8, said process further comprising the steps of

d) cleaving the R^1 silyl group to afford a compound of formula (IV), wherein R^1 is $-\text{H}$; and

30

e) treating with 1,1,1-trichloro-2-methylpropan-2-ol, to afford a compound of formula (IV), wherein R^1 is $-\text{C}(\text{R}^{10}\text{R}^{10})\text{C}(\text{O})_2\text{H}$, and R^{10} is $-\text{CH}_3$.

13. A compound of formula (IV),



(IV)

5 wherein:

R¹ is --Si(R⁹)₃;

10 R², R³, and R⁴ are independently selected from the group consisting of H, C₁₋₃alkyl, -OCH₃, -CF₃, allyl, and halogen;

R⁵ and R⁶ are independently selected from the group consisting of H, phenyl, benzyl, C₁₋₆alkyl, and allyl;

15 each R⁷ is independently selected from -CF₃, C₁₋₃alkyl, -OCH₃, or halogen;

R⁸ is selected from the group consisting of H, -CF₃, and C₁₋₆alkyl;

one of Y and Z is N and the other is S or O;

20

each R⁹ is independently selected from C₁₋₆alkyl, arylC₁₋₆alkyl, or two R⁹ groups together with the silicon atom to which they are attached form a 5-7 membered ring; and

25 n = 0, 1, 2, 3, 4, or 5.

50

14. A compound according to Claim 13, wherein:

R^1 is $-\text{Si}(\text{R}^9)_3$;

5 R^2 is $-\text{CH}_3$;

R^3 , R^4 , R^5 , and R^6 are hydrogen;

n is 2;

10

one R^7 is F in the *ortho* position and the other is $-\text{CF}_3$ in the *para* position;

R^8 is $-\text{CH}_3$;

15 R^9 is C_{1-6} alkyl;

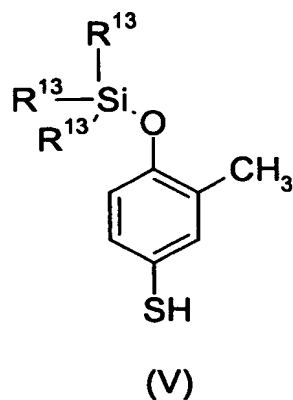
Y is S; and

Z is N.

20

15. A compound according to either one of Claims 13 and 14, wherein R^1 is $-\text{Si}(\text{CH}_3)_2t\text{-Bu}$.

16. A compound of formula (V),



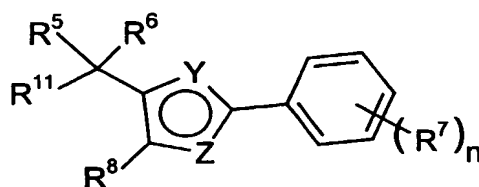
25

wherein:

R^{13} is C_{1-6} alkyl, C_{6-14} aryl C_{1-6} alkyl, or C_{6-14} aryl.

- 5 17. A compound according to Claim 16, wherein two R^{13} are $-CH_3$ and the other is t-Bu.

18. In another aspect of the invention is featured a process for the preparation of compounds of formula (III),



(III)

wherein:

R^5 and R^6 are independently selected from the group consisting of H, phenyl, benzyl, C_{1-6} alkyl, and allyl;

- 15 each R^7 is independently selected from $-CF_3$, C_{1-3} alkyl, $-OCH_3$, or halogen;

R^8 is H, $-CF_3$, or C_{1-6} alkyl;

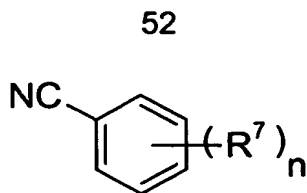
one of Y and Z is N and the other is S or O;

R^{11} is $-OH$; and

$n = 0, 1, 2, 3, 4, \text{ or } 5$;

said process comprising the step of treating a compound of formula (XVII)

- 25 with thioacetic acid,



wherein:

each R^7 is independently selected from $-\text{CF}_3$, $\text{C}_{1-3}\text{alkyl}$, $-\text{OCH}_3$, or halogen;

5 and

$n = 0, 1, 2, 3, 4, \text{ or } 5$.

19. A process according to Claim 18, wherein said process further comprises the step of treating with an α -halo- β -ketoester.

10

20. A process according to Claim 19, wherein said process further comprises the step of treating with a reducing agent.

21. A process according to any one of Claims 18-20, wherein R^5 and R^6 are hydrogen, n is 2, one R^7 is fluorine and the other is $-\text{CF}_3$, R^8 is $\text{C}_{1-6}\text{alkyl}$, Y is S, Z is N, and R^{11} is $-\text{OH}$.

15

22. A process according to any one of Claims 18-21, wherein one R^7 is fluorine in the *ortho* position and the other is $-\text{CF}_3$ in the *para* position, and

20 R^8 is $-\text{CH}_3$.

23. A process according to either one of Claims 18-20, wherein the compound of formula (III) is {2-[2-fluoro-4-(trifluoromethyl)phenyl]-4-methyl-1,3-thiazol-5-yl}methanol.
- 5 24. A process according to any one of Claims 1-12, wherein said compound of formula (I) is treated with an alkyl lithium reagent.